PB84-101674

Pattern Reversal Visual Evoked Potentials in Awake Rats

(U.S.) Health Effects Research Lab.
Research Triangle Park, NC

1983

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TECHNICAL REPORT DATA

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1. REPORT NO. EPA-600/J-83-051	2.
3. PB84-101674	
4. TITLE AND SUBTITLE: Pattern Reversal Visual Evoked Potentials in Awake Rats (Journal Version)	5. REPORT DATE: 1983
	6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S): William Boyes and Robert Dyer	8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS: Neurophysiology Branch, Neurotoxicology Division Health Effects Research Laboratory US Environmental Protection Agency Research Triangle Park, NC 27711	10. PROGRAM ELEMENT NO. ACSL1A
	11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS: Office of Research & Development Health Effects Research Laboratory US Environmental Protection Agency Research Triangle Park, NC 27711	13. TYPE OF REPORT AND PERIOD COVERED
	14. SPONSORING AGENCY CODE EPA-600/11

15. SUPPLEMENTARY NOTES: REF: Brain Research Bulletin, 10:817-823, 1983

16. ABSTRACT

A method for recording pattern reversal evoked potentials (PREPs) from awake restrained rats has been developed. The procedure of Onofrj et al. (26) was modified to eliminate the need for anesthetic, thereby avoiding possible interactions of the anesthetic with other manipulations of interest. Rats were restrained in a harness and placed in front of a pattern generating TV screen displaying a black and white alternating square wave grating. Using various stimulation and recording parameters, normative data are presented from 141 adult male Long-Evans hooded and 11 adult male Sprague-Dawley albino rats. Reliable waveforms were recorded with five identifiable peaks. The labels and mean latencies of these peaks in hooded rats were: N1, 47.3 msec; P1, 65.7 msec; N2, 83.3 msec; P2, 94.4 msec; and N3, 129.9 msec. Spatial acuity functions generated with PREPs gave acuity estimates which corresponded closely to values determined behaviorally for hooded and albino rats.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

REPRODUCED BY
NATIONAL TECHNICAL
INFORMATION SERVICE
US DEPARTMENT OF COMMERCE
SPRINGFIELD VA 22161

18. DISTRIBUTION STATEMENT: Release to Public	19. SECURITY CLASS (This Report): Unclassified	21. NO. OF PAGES: 8
	20. SECURITY CLASS (This page): Unclassified	22. PRICE

EPA-600/J-83-051
JOURNAL ARTICLE

Brain Research Bulletin, Vol. 10, pp. 817–823, 1983. © Ankho International. Printed in the U.S.A.

Pattern Reversal Visual Evoked Potentials in Awake Rats[1]

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Received 30 March 1983

BOYES, W. K. AND R. S. DYER. *Pattern reversal visual evoked potentials in awake rats.* BRAIN RES BULL **10**(6) 817–823, 1983.—A method for recording pattern reversal evoked potentials (PREPs) from awake restrained rats has been developed. The procedure of Onofrj *et al.* [26] was modified to eliminate the need for anesthetic, thereby avoiding possible interactions of the anesthetic with other manipulations of interest. Rats were restrained in a harness and placed in front of a pattern generating TV screen displaying a black and white alternating square wave grating. Using various stimulation and recording parameters, normative data are presented from 141 adult male Long-Evans hooded and 11 adult male Sprague-Dawley albino rats. Reliable waveforms were recorded with five identifiable peaks. The labels and mean latencies of these peaks in hooded rats were: N1, 47.3 msec; P1, 65.7 msec; N2, 83.3 msec; P2, 94.4 msec; and N3, 129.8 msec. Spatial acuity functions generated with PREPs gave acuity estimates which corresponded closely to values determined behaviorally for hooded and albino rats [4,11].

Pattern reversal evoked potentials Awake rats Visual acuity Atropine Hooded vs. albino rats Normative data

PATTERN reversal evoked potentials (PREPs) recorded from awake rats may have many applications. In various species, PREPs have already been used to aid in diagnosis of neurologic disorders [12], to assess spatial or contrast sensitivity [2, 3, 7–10, 15, 18, 19, 21, 26, 29–31], to examine basic properties of the visual system [17,25] and to examine the effects of exposure to neurotoxic compounds [22,24]. However, previous reports of PREPs recorded from rats have employed anesthetized preparations [23, 25, 26], a manipulation which complicates data interpretation in many situations.

This paper describes a simple procedure for recording PREPs from awake rats. The technique is a modification of that of Onofrj *et al.* [26] who used lightly anesthetized preparations. Awake rats were restrained in a harness and placed directly in front of a pattern generating screen. Because the rat eye with a normal-sized pupil has a great depth of field of focus [20], and the reversing pattern dominated the visual field, extensive fixation training or pharmacological immobilization and refraction of the eyes was unnecessary. In this paper, the results of several studies examining the response of the PREP waveform to different stimulation parameters, and its use as a measure of visual acuity are described. In addition, PREPs have been used in our laboratory to study the effects of exposure to several neurotoxicants. The combined control data from these experiments are presented here to examine the across-experiment reliability, and to provide a normative data base for PREPs recorded using a single set of stimulation and recording parameters.

METHOD

Animals

Data from 152 adult male rats are presented. Both Long-Evans hooded (n=141) and Sprague-Dawley albino (n=11) strains obtained from Charles River Breeding Co. were used. At the time of testing, the rats weighed between 250–525 g.

Surgery

At least one week prior to PREP recording, the rats were anesthetized with 0.35 ml/100 g Chloropent (Fort Dodge Lab., Inc) IP for chronic electrode implantation. Stainless steel screw electrodes (00–90 × 1/16 in.) were threaded into the skull. Electrode placement with respect to bregma was: 2 mm anterior and 2 mm to the left and right of midline for the ground and reference electrodes, respectively; and 6 mm posterior and 4 mm to the right of midline for the active recording electrode. In pilot studies, electrode locations near the center of area 17, 6 mm posterior and either 3 or 4 mm lateral, gave much bigger PREP amplitudes than those recorded near the anterior or posterior borders of area 17 [28], confirming Onofrj *et al.*'s [26] report that PREPs are largest over cortical area 17.

Insulated wires were run from the screws to an Amphenol connector and the entire assembly was encased in dental cement. Wound margins were treated with a topical antibiotic, the incision closed with sutures, and each rat given 100,000 units of Penicillin G (IM) post operatively.

[1]This manuscript has been reviewed by the Health Effects Research Laboratory, U.S.E.P.A., and approved for publication. Mention of trade names and commercial products does not constitute endorsement or recommendation for use.

[2]Supported by a National Research Council Research Associateship.

Stimulation Procedure

For PREP recording, each rat was placed in a harness (Alice King Chatham Medical Arts) and positioned with its nose directly facing the TV screen of a Grass model VPG visual pattern generator. The rat's eyes were located either 7 or 15 cm from the screen so that the pattern comprised either 69×74° or 51×58° of visual angle, respectively. Stimuli were black and white horizontal bars (a square wave grating) of various sizes (99% contrast, 30 cd/m² mean luminance at 7 cm) reversed black for white so that there was no overall change in stimulus luminance. Stimulation rate is reported as the number of cycles per second, which corresponds to twice the stimulus reversal rate. In most experiments, evoked potentials were triggered at each pattern shift so that the functional stimulation rate was twice the cycle rate. Pattern reversals and 60 Hz line frequency were nonsynchronized.

In some rats, flash evoked potentials (FEPs) were recorded for comparison. For FEP recording, rats were placed in a chamber with mirrors on three walls and the strobe lamp of a Grass model PS-2 photostimulator on the fourth [13]. Flash intensity was set at 16 which provides a stimulus of approximately 4.53×10^7 Lux peak power.

Recording Procedure

Electroencephalographic activity from the cortical screw electrodes was amplified by 10,000, bandpass filtered from 0.8–100 Hz for the PREP, and 0.8 Hz to 10 kHz for the FEP, displayed on an oscilloscope, and transmitted to a PDP 11/70 computer for signal averaging and data storage. Sample epochs of 400 msec, A/D converted at 2500 Hz, were collected. PREP waveforms were calculated from the average of 200 trials, and FEPs from 64 trials. Evoked potential waveforms were displayed on a Tektronix 4054 graphics terminal where individual peaks were manually selected with a cursor. The computer calculated peak latencies and peak-to-peak amplitudes. Waveform hardcopies were obtained with a Tektronix 4631 printer. Disk storage of all averaged waveforms allowed across-rat group average waveforms to be computed for illustrative purposes, although all statistical group comparisons were performed on individual rat values.

Experimental Protocols

A. Inter-experiment reliability. Five different experiments have been completed in which PREPs were recorded from hooded rats using the same stimulation parameters: 0.20 cycles/degree (cpd), 0.25 Hz, 69×74° field size, and 200 trials average. Each of these five experiments (arbitrarily labeled PST, CTC, DEL, AET, and TOL) was intended to examine the actions of potentially neurotoxic compounds, and employed designs in which groups of exposed rats were compared to controls. For the purposes of examining inter-experiment reliability, data from the control rats are presented here.

B. Temporal frequency. The effect of stimulus reversal rate was investigated in nine hooded rats. PREPs were recorded in each rat to 0.19 cpd gratings reversed at cycle rates of 0.1, 0.25, 0.5, 1.0, 2.5, and 5.0 Hz (69×74° field size). Recording sessions employing the different stimulation rates were presented to each rat in random order.

C. Spatial frequency. Several experiments in which spatial frequency was manipulated have been performed, all employing a field size of 51×58° and 0.25 Hz cycle rate. In two experiments, 32 hooded and 11 albino rats were stimulated with patterns of 0.03, 0.05, 0.10, 0.20 and 0.44 cpd. Further experiments on hooded rats (n=43) employed spatial frequencies of 0.10, 0.20, 0.40, and 0.79 cpd. Also in these experiments, 200 trials of random EEG activity were averaged while the animal watched a stationary (nonreversing) pattern to obtain a measure of the average recording noise level.

FIG. 1. Hypothetical noise and signal-plus-noise curves. By selecting the largest peak-to-peak amplitudes as is normally done, the experimenter is picking the maximum amplitude of noise along with the maximum amplitude of signal.

Visual acuity estimates were made using a modification of published procedures in which the amplitude-spatial frequency function is extrapolated to the averaged EEG noise level to estimate the limits of acuity [2, 3, 29]. Other investigators have estimated spatial or contrast sensitivity in a variety of species [2, 3, 29] by extrapolating the falling limb of the amplitude function to zero to achieve the theoretical limit of resolution [2, 3, 15, 29]. Depending upon the peak selection procedure and the amount of noise in the averaged evoked potential, extrapolation to zero may overestimate the acuity limit, whereas extrapolation to the noise level provides a more accurate estimate. This is a result of the interplay among signal, noise and the peak selection criteria. Every averaged evoked potential contains signal plus noise. By selecting the largest peak-to-peak amplitudes (i.e., the maxima and minima within time windows), as is normally done, the experimenter necessarily selects the maximum amplitude of noise along with the maximum amplitude of signal. This is demonstrated in Fig. 1. If the highest peak and the lowest valley are always picked, then the peak-to-peak amplitude is measured at the point where the noise amplitude is maximal along with the point where the signal amplitude is maximal. If the noise had been maximal at a slightly different moment, then that would have been the peak or valley selected. By doing so, the noise no longer has a random distribution, but has been selected to be maximal. In many applications, such as comparing evoked potentials from one group to another where the noise levels in each group are equal, the implications of this phenomenon may be ignored. But when extrapolating to zero, the addition of noise to the signal amplitudes can lead to overestimates of the limits of resolution. The amount of the overestimate is inversely related to the signal-to-noise ratio. However, if the acuity estimates are instead extrapolated to the averaged noise level, then for any number of trials averaged, the acuity estimate remains constant. This estimate represents the true acuity

limit because the noise level is a constant value added to every point along the acuity function.

D. Topical atropine. To help assure that the PREP method of estimating spatial acuity was valid, the effect of pupil dilation with atropine, which should decrease the depth of field of focus [20] and thereby decrease acuity, was investigated. Thirty hooded rats received a topical ocular drop of either distilled water (n=17), or 1% atropine sulphate dissolved in distilled water (n=13) 30 min before the onset of PREP testing. Pupil diameter at the time of testing was examined with an ophthalmoscope. PREPs to patterns of 0.10, 0.20, 0.40, and 0.79 cpd (51×58° field size), and the noise condition described above were recorded from each rat. Pattern size testing order was counterbalanced across animals.

E. Statistical procedures. In experiments requiring statistical analysis, the analysis involved first a MANOVA including 4 peak-to-peak amplitudes and 5 peak latencies as dependent variables. A statistically significant MANOVA ($p<0.05$) was followed by individual ANOVAs on each peak latency and peak-to-peak amplitude. To maintain an overall probability level of $\alpha=0.05$, the probability level was divided by the number of ANOVAs performed in accordance with the Bonferroni correction procedure ($p=0.05/9=0.0056$).

RESULTS

The major characteristic of the rat PREP waveform is a positive wave complex followed by a negative wave complex. Three representative PREP waveforms, two averaged from individual rats and one averaged across a group of rats, along with a group average FEP from the same rats, are presented in Fig. 2. Five reliably identifiable peaks in the PREP waveforms have been labeled. At lower stimulation rates (1 Hz or less), two positive peaks, P1 and P2, can be identified in the large positive wave. The PREPs of most rats resemble that of Rat ORT18 in Fig. 2 with P1 being larger than P2, however in some rats (~30%) P2 is larger, as is the case for Rat ORT6. In general, the PREP has a later onset than the FEP and is approximately one half the amplitude. The PREP also differs from the FEP in that the major initial peak is positive rather than negative in polarity.

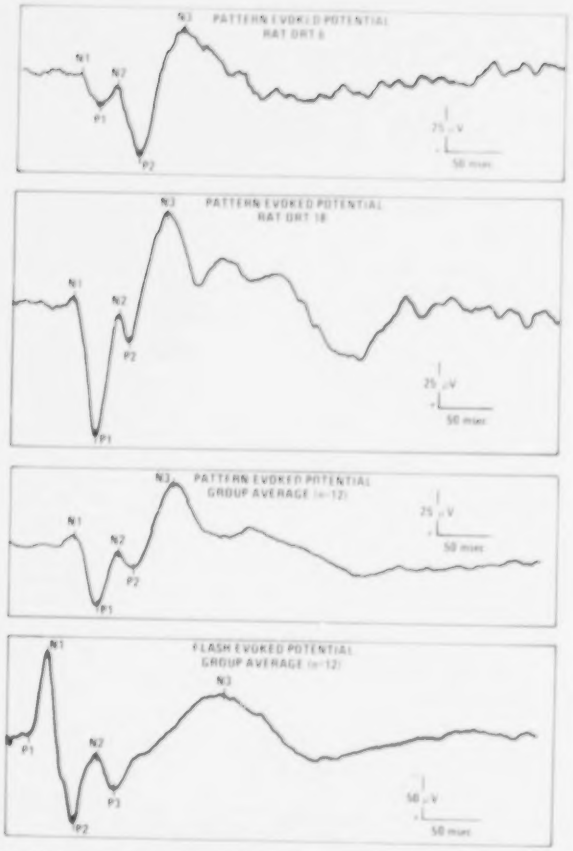

FIG. 2. Sample waveforms. The top two waveforms are PREPs recorded from two individual hooded rats using the stimulation and recording parameters described in the text for the AET experiment. The third trace is the product of averaging together 12 individual control rat PREPs from the AET study. The bottom trace is the group averaged FEP recorded from the same rats.

Inter-Experiment Reliability

Control data from 5 experiments in which PREPs were recorded using the same set of stimulation parameters (0.20 cpd, 0.25 Hz cycle rate, 69×72° field size, 200 trials average), are summarized in Table 1. Table 1a contains peak latency data and Table 1b peak-to-peak amplitude data. The across study means and standard errors of the mean, calculated from the individual experiment means, give an indication of the reliability over time (approximately 6 months), across different groups of rats, and across peak selection criteria of several individual experimenters and technicians. In general, the latencies show a high degree of reliability with the across experiment standard error being 1–4% of the mean. The peak-to-peak amplitudes are somewhat more variable, with standard errors of the mean ranging from 7% for N1P1 to 25% of the mean for N2P2.

Temporal Frequency

Group average PREP waveforms recorded at different stimulation frequencies are presented in Fig. 3. Increases in stimulation frequency produced increases in the latency of all the PREP peaks, although the increases were statistically significant for only peaks N1 and P1, both F's(5,53)>5.70, both p's<0.0003. No significant changes in peak-to-peak amplitude were produced by changes in stimulation rate. At some frequencies (0.1, 0.5, and 1.0 Hz), a negative peak later than N3 also appears to be present. This peak was evident in some individual animal recordings as well as in the group average waveform, but was not selected for analysis. At 2.5 Hz, the N2P2 wave was greatly reduced. At 5 Hz, the character of the waveform began to change to that of a steady state response [26].

Spatial Frequency

Combined data from 32 hooded rats and 11 albino rats, recorded at 5 spatial frequencies (0.25 Hz temporal frequency), are presented in Fig. 4. At each spatial frequency, the albino group PREP is smaller in amplitude and less well defined than that of the hooded rats. In addition, the albino waveform cannot be discriminated from noise at spatial frequencies between 0.2 and 0.44 cpd, whereas the hooded rat PREP is still evident at 0.44 cpd. The N2 peak was not iden-

TABLE 1a

CONTROL GROUP MEANS IN SEVERAL EXPERIMENTS USING THE SAME STIMULATION PARAMETERS

Experiment	n	Body Weight Mean ± SE	PREP Latencies (msec) N1 Mean ± SE	P1 Mean ± SE	N2 Mean ± SE	P2 Mean ± SE	N3 Mean ± SE
AET	14	307 ± 10	46.5 ± 1.0	63.6 ± 0.8	78.1 ± 1.2	90.1 ± 1.7	131.0 ± 5.6
PST	16	372 ± 11	49.2 ± 1.0	64.2 ± 0.5	81.8 ± 1.6	92.5 ± 1.9	119.6 ± 4.2
CTC	12	461 ± 11	44.8 ± 1.9	66.6 ± 0.9	86.1 ± 2.5	100.3 ± 5.8	142.3 ± 9.5
TOL	12	494 ± 14	48.5 ± 1.1	67.7 ± 1.2	82.5 ± 2.4	88.0 ± 2.6	115.9 ± 3.9
DEL	11	410 ± 13	47.5 ± 0.9	66.3 ± 0.9	88.1 ± 2.8	101.1 ± 4.0	140.2 ± 8.9
Across Study Mean, SE			47.3 ± 0.77	65.7 ± 0.77	83.3 ± 1.74	94.4 ± 2.67	129.8 ± 5.31

TABLE 1b

CONTROL GROUP MEANS IN SEVERAL EXPERIMENTS USING THE SAME STIMULATION PARAMETERS

Experiment	n	PREP Amplitudes (μV) N1 P1 Mean ± SE	P1 N2 Mean ± SE	N2 P2 Mean ± SE	P2 N2 Mean ± SE
AET	14	27.0 ± 2.8	24.5 ± 2.9	20.1 ± 4.8	39.3 ± 6.6
PST	16	24.8 ± 4.0	23.5 ± 3.7	10.3 ± 2.2	26.5 ± 3.3
CTC	12	27.9 ± 3.5	24.1 ± 3.8	11.2 ± 3.1	22.5 ± 2.6
TOL	12	27.1 ± 5.0	17.4 ± 4.0	2.5 ± 0.8	22.7 ± 4.0
DEL	11	36.2 ± 7.7	35.2 ± 8.0	13.0 ± 4.2	26.1 ± 5.0
Across Study Mean, SE		28.6 ± 1.97	24.9 ± 2.87	11.4 ± 2.82	27.4 ± 3.08

tified in albinos, and was reduced at both high and low spatial frequencies in hooded rats.

Figure 5 presents a plot of group mean P2N3 peak-to-peak amplitudes of PREPs recorded from hooded rats stimulated with a broad range of spatial frequencies. The amplitude-spatial frequency function of hooded rats was basically flat from 0.05 to 0.40 cpd, and fell rapidly at higher spatial frequencies. Linear extrapolation of the descending limb of the function to zero gave a higher acuity estimate, about 2.0 cpd, than extrapolating to the measured average EEG noise level, about 1.36 cpd. No a priori reason was developed for selecting a particular peak-to-peak amplitude for use in estimating the limits of visual acuity. Group acuity functions based on P1N3 amplitude were similar in shape, larger in amplitude, and gave comparable acuity estimates to those based on P2N3 amplitude. The other peak-to-peak amplitudes, however, were smaller in magnitude, and gave highly variable estimates of acuity after extrapolation to noise levels.

Individual rat acuity functions have been obtained from 28 hooded rats using either P1N3 or P2N3 amplitudes, whichever was larger for that rat. The frequency distribution of acuity limit values based upon extrapolation to the EEG noise level is presented in Fig. 6. The distribution is markedly skewed toward higher values, a few rats having relatively large estimates using this method. The mean, mode and median values of the distribution in Fig. 6 are 1.42, 0.82, and 1.20 cpd, respectively.

Topical Atropine

At the time of PREP testing, 30 min after eye drop administration, hooded rats treated with distilled water had pupils of approximately 1 mm diameter, and rats treated with atropine had fully dilated pupils of approximately 3–4 mm diameter. Group average PREP waveforms recorded at several pattern sizes and averaged EEG noise are presented in Fig. 7. The measured dependent variables were N1, P1, N2, P2, and N3 latencies and N1P1, P1N2, N2P2, and P2N3 amplitudes. The overall MANOVA showed statistically significant changes in PREP values related to dose, $F(9,19)=2.67$, $p=0.03$, pattern size, $F(27,244)=3.45$, $p=0.0001$, and dose × pattern size interaction, $F(27,244)=1.74$, $p=0.0163$. After Bonferroni correction, the only individual ANOVA showing significant dose-related changes was for peak P1 latency, which showed an altered dose × pattern size interaction, $F(3,119)=5.14$, $p=0.0027$. P1 latency in the atropine group was later at low spatial frequencies, and earlier at high spatial frequencies than the control group. Two parameters, N1P1 and P2N3 peak-to-peak amplitudes, showed significant pattern size effects without regard to dosage, both F's$(3,19)>13.37$, both p's<0.0001.

DISCUSSION

This series of studies demonstrates that PREP waveforms can be reliably recorded from awake restrained rats. Five

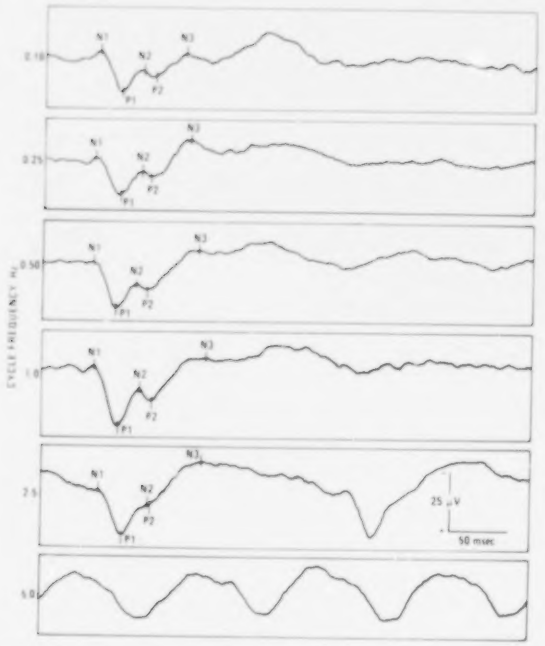

FIG. 3. PREPs as a function of stimulation frequency. Each waveform is the group average of 9 hooded rats.

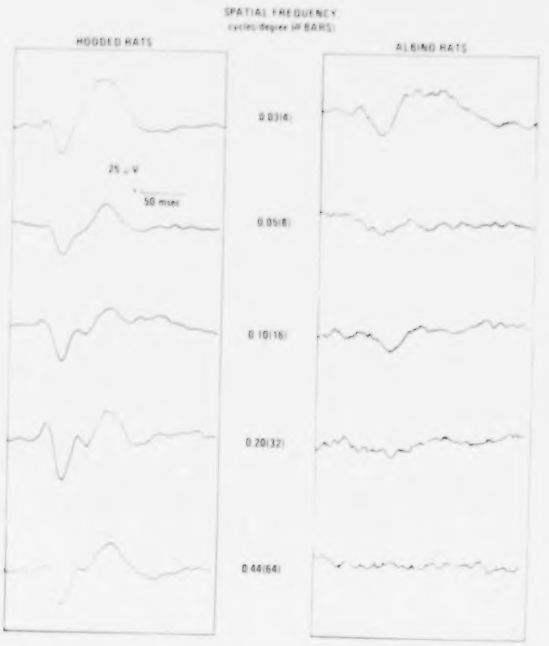

FIG. 4. Comparison of PREPs recorded from hooded and albino rats at different spatial frequencies (0.25 Hz temporal frequency). Each trace is a group average waveform calculated from 32 hooded or 11 albino rats.

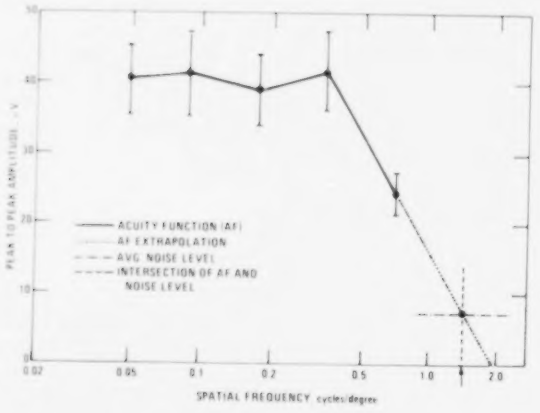

FIG. 5. Group acuity function in one representative group of five hooded rats. Each point represents the P2N3 peak-to-peak amplitude (mean ± SEM). Extrapolation of the acuity function to the noise level yields an acuity estimate of about 1.36 cpd whereas extrapolation to zero yields an estimate of about 1.8 cpd.

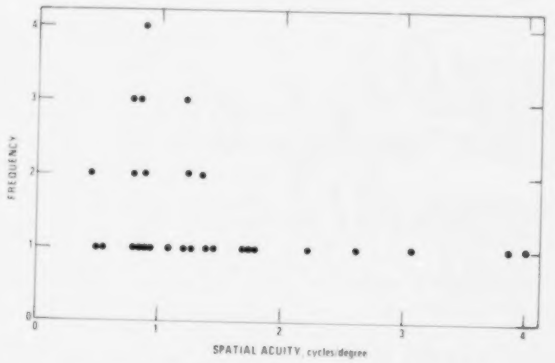

FIG. 6. Frequency distribution of individual rat acuity limit values for 28 hooded rats. Acuity limit values were determined by extrapolation to the measured noise level of PREP acuity functions using the larger of either P1N3 or P2N3 amplitude.

identifiable peaks have been documented. The peak latencies and peak-to-peak amplitudes of the PREP were generally stable across studies. This was particularly true of the P1 component which showed an across studies latency SEM of roughly 1% of the mean. The N2P2 component, although stable in latency, was small and variable in amplitude. It was difficult to identify in the averaged waveforms of some individual rats, although it was quite prominent in others. In the group average waveforms, the N2P2 component was present at 1.0 Hz, but disappeared at higher stimulation frequencies, and was reduced at low or at high spatial frequencies. While the volatile nature of the N2 and P2 peaks may make them unsuitable for certain applications, they may be somewhat more sensitive to toxicant-induced visual system damage

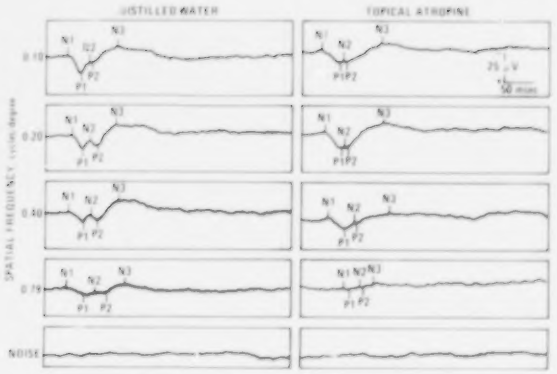

FIG. 7. The effects of topical atropine on hooded rat PREPs recorded to different spatial frequencies. Each trace is a group average PREP recorded 30 min after application of either distilled water (n = 17), or 1.0% atropine sulphate (n = 13) to both eyes. Pupil diameter at the time of testing was approximately 1 mm in the distilled water group and 3–4 mm in the atropine group. The "noise" condition is random EEG (no eliciting stimulus) averaged over the same number of trials as the PREPs. Atropine treatment produced a statistically significant changes in peak P1 latency, but no reliable dose-related changes in peak-to-peak amplitudes.

than the other peaks [6]. Conversely, the atropine study showed no statistically significant dose-related change in peak-to-peak amplitudes, but a significant dose × pattern size-induced change in peak P1 latency. Contrary to expectations, spatial acuity, as measured by the extrapolation of peak-to-peak amplitudes was not affected by atropine. This suggests that peak latencies may be a more sensitive measure of altered vision than peak-to-peak amplitudes.

Compared to the FEP the PREP is about half the amplitude, has a later onset, the opposite polarity of the initial component, and a different overall morphology. The PREP amplitude is smaller in albino than hooded rats, the reverse of the case for the FEP [14]. These findings confirm previous reports that the rat PREP and FEP are clearly different responses [26].

The awake rat PREP waveform reported here resembles those recorded from both anesthetized rats [23,26] and from awake humans [32]. Both rat and human PREP waveforms are largest over the specific visual projection areas [16], and both are characterized by a major positive wave [23, 26, 32]. The latency of the more prominent peak in the positive wave of the awake rat PREP is about 65 msec, and that of humans is about 100 msec [32]. Considering the vast differences in the anatomy of the rat and human visual systems, the PREP waveforms are surprisingly similar. This suggests, but does not prove, that rat and human PREPs reflect analogous processes. Although the human PREP to small pattern sizes is thought to reflect primarily the activation of foveal cells [16], larger patterns probably activate the peripheral human retina [16]. The peripheral retinas of rats and humans are similar but the rat retina mimics the human fovea very poorly. Thus, the rat PREP may be a better model of the human PREP when obtained using large rather than small sized patterns.

The general morphology of the rat PREPs presented here resembles previous reports [26], but the previous peak latencies were later (85.5 vs. 65.7 msec, for the major positive peak) and the amplitudes smaller (6.6 vs. 28.6 μV, for the equivalent to N1P1) than those reported here. In addition, the small N2P2 component was not identified previously. These differences are most likely due to slowing and diminution of the response produced by the barbiturate anesthetic employed during recording in the previous report, but other procedural differences such as the brighter stimuli (60 vs. 30 cd/m²), and larger field size (120×120° vs. 69×74°) employed previously may also have contributed to such differences. Ethrane anesthesia reduces the amplitude of PREPs in human children, although latencies were not reported [1]. Nevertheless, since in both awake and anesthetized cases the waveshape consists of a major positive followed by a major negative component, and the responses to manipulations of spatial and temporal frequency were qualitatively similar, common processes probably contributed to both responses.

Acuity estimates obtained by extrapolation of the rat amplitude-spatial frequency functions to measured EEG noise levels revealed a distribution of acuity limit values with a median value of 1.2 cpd. This corresponds exactly to the value for hooded rats obtained by Birch and Jacobs [4] in behaviorally conducted psychophysical experiments. In addition, those authors reported the limits of spatial resolution in albino rats to be 0.34–0.43 cpd. The present finding that albino rat PREPs cannot be distinguished from noise at 0.20 or 0.44 cpd is consistant with their findings. Behavioral psychophysical experiments require weeks or months of training. In contrast, PREPs require only an hour or so of surgery a week ahead of time, and about an hour of testing to obtain an acuity estimate. The vast time saving in combination with the apparent accuracy of PREP acuity measures may allow acuity estimates to be performed in applications previously prohibitive.

ACKNOWLEDGEMENTS

The authors thank M. Bercegea, M. Geboff, I. Harrell and D. Jenkins for technical assistance, and I. Bodis-Wollner, C. Harnois and M. Onofrj for helpful discussions.

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